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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,563	12/10/2003	Theresa O'Keefe	10448-213001 / MPI01-244P	9540

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/733,563	O'KEEFE ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-8 are cancelled.

Claims 10 and 11 have been amended.

2. Claims 9-12 are pending and under consideration.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Rejections

4. The rejection of claims 9-12 under 35 U.S.C. 103(a) as being unpatentable over LaRosa et al [a] (US Patent 6,727,349 B1, priority to 2/3/2000) in view of Bonnefoy et al (WO 99/58679, 11/18/1999) is withdrawn in view of Applicants' statement that "At the time the claimed invention was made, both LaRosa et al [a] and LaRosa et al [b] were owned by, or subject to an obligation of assignment to, Millennium Pharmaceuticals, Inc (as evidenced by assignments recorded at reel/frame 011196/0894 and 012511/0380, respectively), and the claimed invention was subject to an obligation of assignment to Millennium Pharmaceuticals, Inc." filed 10/12/2007

5. The rejection of claims 9-12 under 35 U.S.C. 103(a) as being unpatentable over LaRosa et al [b] (US Patent 6,696,550 B2, priority to 2/3/2000) in view of Bonnefoy et al (WO 99/58679, 11/18/1999) is withdrawn in view of Applicants' statement that "At the time the claimed invention was made, both LaRosa et al [a] and LaRosa et al [b] were owned by, or subject to an obligation of assignment to, Millennium Pharmaceuticals, Inc (as evidenced by assignments recorded at reel/frame 011196/0894 and 012511/0380, respectively), and the claimed invention was subject to an obligation of assignment to Millennium Pharmaceuticals, Inc." filed 10/12/2007

6. The rejection of claims 9-12 under 35 U.S.C. 103(a) as being unpatentable over Hancock et al (US 2002/0042370 A1, filed 4/13/2001, IDS reference AA filed 11/14/05) in view of Bonnefoy et al (WO 99/58679, 11/18/1999, previously cited on PTO-892 mailed 2/14/06) is withdrawn in view of Applicants' statement that "At the time the

claimed invention was made, both Hancock et al. and Horvath et al. were owned by, or subject to an obligation of assignment to, Millennium Pharmaceuticals, Inc (as evidenced by assignments recorded at reel/frame 012190/0951 and 012006/0037, respectively), and the claimed invention was subject to an obligation of assignment to Millennium Pharmaceuticals, Inc." filed 10/12/2007.

7. The rejection of claims 9-12 under 35 U.S.C. 103(a) as being unpatentable over Horvath et al [b] (US Patent 6,663,863 B2, priority at least to 3/15/2001, cited on PTO-892 mailed 7/21/06) in view of Bonnefoy et al (WO 99/58679, 11/18/1999, previously cited on PTO-892 mailed 2/14/06) is withdrawn in view of Applicants' statement that "At the time the claimed invention was made, both Hancock et al. and Horvath et al. were owned by, or subject to an obligation of assignment to, Millennium Pharmaceuticals, Inc (as evidenced by assignments recorded at reel/frame 012190/0951 and 012006/0037, respectively), and the claimed invention was subject to an obligation of assignment to Millennium Pharmaceuticals, Inc." filed 10/12/2007.

Rejections Maintained

8. The rejection of claims 9-12 under 35 U.S.C. 103(a) as being unpatentable over LaRosa et al [c] (WO 01/57226 A1, published 8/9/2001) in view of Bonnefoy et al (WO 99/58679, 11/18/1999, previously cited on PTO-892 mailed 2/14/06) is maintained.

The response filed 10/12/2007 argues the specific teachings of the individual references stating that LaRosa et al [c] do not teach a preference for any particular isotype for the heavy chain constant region or even any particular IgG1 allotype and there is no suggestion in LaRosa et al [c] that the CCR2 specificity should be combined with the ability or inability to fix complement. Applicant states that the humanized antibody of Bonnefoy comprising the mutated human IgG1 constant region of SEQ ID NO:110 is a completely different humanized antibody that binds a completely different target than the claimed CCR2 humanized antibody and there is no motivation in Bonnefoy to select the specific IgG1 human heavy chain constant region of SEQ ID

NO;110, nor the human kappa light chain constant region of SEQ ID NO:113 to produce the claimed humanized CCR2-specific antibodies. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In response to applicant's argument that the humanized antibody of Bonnefoy comprising the mutated human IgG1 constant region of SEQ ID NO:110 is a completely different humanized antibody that binds a completely different target than the claimed antibodies, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, LaRosa et al [c] teach the claimed humanized CCR2 specific antibody and antigen-binding fragments thereof that inhibit ligand binding for treating a variety of human disorders in which activation of CCR2 is implicated and according to Bonnefoy, if a non-cytotoxic blocking antibody is required it is preferable to modify the generally more stable IgG1, specifically a modified human IgG1 constant region comprising two mutations ($Leu^{235} \rightarrow Ala^{235}$ and $Gly^{237} \rightarrow Ala^{237}$), identical to the claimed human IgG1 constant region of SEQ ID NO:110. Thus, while the art does recognize a subgenus of heavy chain constant region isotypes as noted by applicant, the prior art specifically teaches and suggests the desirability of using human

IgG1 comprising $Leu^{235} \rightarrow Ala^{235}$ and $Gly^{237} \rightarrow Ala^{237}$ mutations (i.e., SEQ ID NO;110) as a stable non-cytotoxic blocking antibody. Therefore, one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to modify the ligand blocking humanized CCR2 antibody of LaRosa et al [c] with the modified human IgG1 constant region as taught by Bonnefoy to produce a stable humanized non-cytotoxic CCR2 blocking antibody for the treatment of human disorders in which activation of CCR2 is implicated.

Applicants' again refers to unrelated U.S. Patent 6,682,736 as disclosing a preference for completely different constant regions is acknowledged, however, the instant rejection is based on the combined teachings of LaRosa et al [c] and Bonnefoy et al. As discussed supra, Bonnefoy et al teach the modified human IgG1 constant region of SEQ ID NO:110 and the desirability of using SEQ ID NO:110, particularly for a ligand blocking antibody such as the humanized CCR2 antibody of LaRosa et al [c] and the relevance of unrelated U.S. Patent 6,682,736 remains unclear. Applicant has not presented a basis establishing why one of ordinary skill in the art when presented with U.S. Patent 6,682,736 would have been led away from using human IgG1 comprising $Leu^{235} \rightarrow Ala^{235}$ and $Gly^{237} \rightarrow Ala^{237}$ mutations (i.e., SEQ ID NO;110) given the desirability of said human IgG1 as articulated by Bonnefoy et al (supra), particularly where U.S. Patent 6,682,736 does not criticize, discredit, or otherwise discourage the solution claimed...." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and the rejection is maintained.

9. The rejection of claims 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horvath et al [a] (WO 01/70266 A2, published 9/27/200, cited on

PTO-892 mailed 7/21/06) in view of Bonnefoy et al (WO 99/58679, 11/18/1999, previously cited on PTO-892 mailed 2/14/06) is maintained.

The response filed 10/12/2007 reviews the specific teachings of the individual references and acknowledges that Horvath et al [a] teach the humanized CCR2 antibody, except Horvath et al [a] do not teach the modified human IgG1 heavy chain constant region sequence of SEQ ID NO:110. Applicant states that the references do not teach a preference for any particular isotype for the heavy chain constant region or even any particular IgG1 allotype and there is no suggestion in Horvath et al [a] that the CCR2 specificity should be combined with the ability or inability to fix complement. Applicant states that the humanized antibody of Bonnefoy comprising the mutated human IgG1 constant region of SEQ ID NO:110 is a completely different humanized antibody that binds a completely different target than the claimed CCR2 humanized antibody and there is no motivation in Bonnefoy to select the specific IgG1 human heavy chain constant region of SEQ ID NO;110, nor the human kappa light chain constant region of SEQ ID NO:113 to produce the claimed humanized CCR2-specific antibodies. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In response to applicant's argument that the humanized antibody of Bonnefoy comprising the mutated human IgG1 constant region of SEQ ID NO:110 is a completely different humanized antibody that binds a completely different target than the claimed antibodies, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce

the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Horvath et al [a] teach the claimed humanized CCR2 specific antibody and antigen-binding fragments thereof that inhibit ligand binding for treating a variety of human disorders in which activation of CCR2 is implicated and according to Bonnefoy, if a non-cytotoxic blocking antibody is required it is preferable to modify the generally more stable IgG1, specifically a modified human IgG1 constant region comprising two mutations ($Leu^{235} \rightarrow Ala^{235}$ and $Gly^{237} \rightarrow Ala^{237}$), identical to the claimed human IgG1 constant region of SEQ ID NO:110. Thus, while the art does recognize a subgenus of heavy chain constant region isotypes as noted by applicant, the prior art specifically teaches and suggests the desirability of using human IgG1 comprising $Leu^{235} \rightarrow Ala^{235}$ and $Gly^{237} \rightarrow Ala^{237}$ mutations (i.e., SEQ ID NO;110) as a stable non-cytotoxic blocking antibody. Therefore, one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to modify the ligand blocking humanized CCR2 antibody of Horvath et al [a] with the modified human IgG1 constant region as taught by Bonnefoy to produce a stable humanized non-cytotoxic CCR2 blocking antibody for the treatment of human disorders in which activation of CCR2 is implicated. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

Applicant again refers to unrelated U.S. Patent 6,682,736 as disclosing a preference for completely different constant regions is acknowledged, however, the instant rejection is based on the combined teachings of Horvath et al [a] and Bonnefoy et al. As discussed supra, Bonnefoy et al teach the modified human IgG1 constant region of SEQ ID NO:110 and the desirability of using SEQ ID NO:110, particularly for a

ligand blocking antibody such as the humanized CCR2 antibody of Horvath et al [a] and the relevance of unrelated U.S. Patent 6,682,736 remains unclear. Applicant has not presented a basis establishing why one of ordinary skill in the art when presented with U.S. Patent 6,682,736 would have been led away from using human IgG1 comprising $Leu^{235} \rightarrow Ala^{235}$ and $Gly^{237} \rightarrow Ala^{237}$ mutations (i.e., SEQ ID NO;110) given the desirability of said human IgG1 as articulated by Bonnefoy et al (supra), particularly where U.S. Patent 6,682,736 does not criticize, discredit, or otherwise discourage the solution claimed...." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and the rejection is maintained.

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by

telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643